AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

24353 7590 08/26/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,842	BRIESEWITZ ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18,22-26,30-34,36 and 39-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18,22-26,30-34 and 36* is/are rejected.

7)☒ Claim(s) *39-56* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 16-18, 22-26, 30-34, 36, and 39-56 are pending.

2. The following new grounds of objection and rejections are necessitated by the amendment filed 6/3/04.

3. Claim 24 is objected to because "targeting moieties" in line 5 does not correspond to "a targeting moiety" in line 4.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 16-18, 22-26, 30-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a host, said method comprising: administering to said host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and a targeting moiety that binds to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said targeting moiety is a peptidyl-prolyl isomerase ligand for FKBP or cyclophilin selected from the group consisting of FK506, rapamycin and cyclophilin, said bifunctional molecule exhibits a modulated biodistribution upon administration to said host as compared to a free drug control, and to direct the biodistribution of said drug to an intracellular space as compared to a free drug control, (2) the said method wherein the bifunctional molecule exhibits enhanced efficacy and reduced toxicity upon administration to said host. (3) The said method wherein the bifunctional molecule further comprises a linking group, (4) The said method wherein the bifunctional molecule does not include a linking group, (5) the said method wherein the bifunctional molecule is administered as a pharmaceutical preparation, (6) the said method wherein the host is a mammalian host such as human, **does not** reasonably provide enablement for a method as set forth in claims 16-18, 22-26, 30-34, and 36 wherein the targeting moiety of the bifunctional molecule is any molecule that

binds to all intracellular biodistribution modulating protein, and wherein the drug moiety of the bifunctional molecule is any "small molecule", or any "drug derivative" for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only bifunctional molecule having a drug of interest such as doxorubicin, methotrexaste, vincristine, etoposide covalently linked through a targeting moiety such as FK506 or rapamycin that binds to an intracellular biodistribution modulating protein such as FKBP as a method for directing the biodistribution of a drug upon administering to a host.

The specification does not teach how to make all bifunctional molecules for the method as set forth in claims 16-18, 22-26, 30-34, and 36 for the following reasons: The claimed method encompasses all bifunctional molecules having a molecule weight that does not exceed about 5000 daltons comprising any targeting moiety optionally joined to any drug moiety such as any active drug derivative, and any small molecule.

There is insufficient guidance as to the structure of *all* "targeting molecule" of the bifunctional molecule that binds to all "intracellular biodistribution modulating protein", and all "drug active derivative thereof" and "small molecule" of the bifunctional molecule for the claimed method without the amino acid sequence, let alone how to make all the targeting molecule for the claimed method. It is known that not all drug targeting to intracellular space is effective for treating all disease. Further, there is insufficient guidance as to which undisclosed "small molecule", and "derivative" of which drug is effective for targeting to which intracellular space when optionally joined by a linking group to any targeting moiety that binds to all intracellular biodistribution modulating protein.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Without the specific amino acid sequence of any drug, and active derivative thereof, and any targeting moiety, one skill in the art cannot make, much less use the claimed method.

Briesewitz *et al,* of record, teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Further, the term "comprising" in claims 24 and 30 expands the bifunctional molecule to include additional amino acids at either or both ends. Given the indefinite number of undisclosed targeting moiety, either linked or not linked to any drug derivative and any small molecule in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety is effective for which undisclosed small molecule and drug derivative in the bifunctional molecule having a molecular weight that does not exceeds about 5000 daltons, in turn, would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 6/3/04 have been fully considered but are not found persuasive.

Applicants' position is that the bifunctional molecules employed in the subject methods are extensively described in the specification beginning at page 4 of the specification. This includes a generic description of these molecules, a detailed description of these molecules in terms of formulas, an extensive description of each of the component pads of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23). In addition, a detailed description of how to make the targeted bifunctional molecules is provided at pages 24 to 28 of the specification, where specific guidance is provided on how to make the compounds. Three representative methods of making the compounds are described. Furthermore, page 26 provides even more detail regarding bifunctional molecules of the invention that include a peptidyl-prolyl isomerase-targeting moiety. Guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed methods is provided on page 25. The FK506, rapamycin, cyclosporin A and the like… on page 21 lines 3 to 5 of the specification are representative ligands capable of serving as the z moiety (targeting moiety) and not the drug moiety. (2) Each component of the bifunctional molecule, e.g., drug moieties (page 6 to 16), targeting moiety (page 16 to21) and linking moiety (pages 22 to 23) as well as how to make these targeted bifunctional molecules (page 24 to 28) are fully described in the specification without undue experimentation. As such, the amount of experimentation necessary is not undue in view of the guidance provided by the specification. Though time-consuming, it is well within the skill of the ordinary practitioner to obtain a drug moiety and a targeting moiety as claimed, and to link them to form a bifunctional molecule (with or without a linker moiety) as taught in the specification, using well known methods of synthetic organic chemistry. Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed, nor that examples be "working" examples. No more is needed than that the invention be disclosed in such a manner that one skilled in the ad would be able to practice the invention without undue experimentation.

However, the claimed method encompasses all bifunctional molecules having a molecule weight that does not exceed about 5000 daltons comprising any targeting moiety optionally joined to any drug moiety such as any active drug derivative, and any small molecule.

There is insufficient guidance as to the structure of *all* "targeting molecule" of the bifunctional molecule that binds to all "intracellular biodistribution modulating protein", and all "drug active derivative thereof" and "small molecule" of the bifunctional molecule for the claimed method without the amino acid sequence, let alone how to make all the targeting

molecule for the claimed method. It is known that not all drug targeting to intracellular space is effective for treating all disease. Further, there is insufficient guidance as to which undisclosed "small molecule", and "derivative" of which drug is effective for targeting to which intracellular space when optionally joined by a linking group to any targeting moiety that binds to all intracellular biodistribution modulating protein.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Without the specific amino acid sequence of any drug, and active derivative thereof, and any targeting moiety, one skill in the art cannot make, much less use the claimed method.

Briesewitz *et al,* of record, teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Further, the term "comprising" in claims 24 and 30 expands the bifunctional molecule to include additional amino acids at either or both ends. Given the indefinite number of undisclosed targeting moiety, either linked or not linked to any drug derivative and any small molecule in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety is effective for which undisclosed small molecule and drug derivative in the bifunctional molecule having a molecular weight that does not exceeds about 5000 daltons, in turn, would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

The drug moiety of the bifunctional molecule may be the whole compound or a derivative thereof. e.g. its binding fragment or portion thereof that retains its affinity and activity for the target of interest. The drug moiety is capable of interacting with a target … where such targets may be proteins, phospholipids, nucleic acids and the like where proteins are of- particular interest. Specific protein targets of interest include- without limitation enzymes, e.g. kinases- phosphatases- reductases, Cyclooxygenases proteases and the like. The specification on page 21 discloses that ligands capable of serving as the Z moiety (targeting moiety) of the bi functional

include ligands the intracellular proteins. Such as: peptidyl-prolyl isomerase ligands- e.g. 17 14.506- rapamycin, cyclosporin A and the like.

It is not clear the protein target such as "and the like", the derivative thereof and fragment thereof in the drug moiety as well as the targeting moiety of the bifunctional molecule is effective for the claimed method given that the specific biodistribution modulating protein to which the targeting moiety binds may vary greatly depending on the desired biodistribution of the bifunctional molecule and the undisclosed drug moiety component thereof. Further, the biodistribution modulating protein may have one or more modified residues (page 17, lines 16-20). Given the indefinite number of undisclosed targeting moiety, linked or not linked to any drug derivative and any small molecule in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety is effective for which undisclosed small molecule and drug derivative in the bifunctional molecule, in turn, would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

6. Claims 16-18, 22-26, 30-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all drug derivative (claim 16), all drug wherein the drug is any "small molecule" (claim 33) and all targeting moiety that binds to all endogenous biodistribution modulating proteins of the functional molecule in the claimed method as set forth in claims 16-18, 22-26, 30-34, and 36.

The specification discloses only bifunctional molecule having a drug of interest such as doxorubicin, methotrexate, vincristine, etoposide covalently linked through a targeting moiety such as FK506 or rapamycin that binds to an intracellular biodistribution modulating protein such as FKBP as a method for directing the biodistribution of a drug upon administering to a host.

With the exception of the specific method of directing the biodistribution of a drug using the specific targeting moiety FK506 or rapamycin of the bifunctional molecule that binds to an

intracellular biodistribution modulating protein such as FKBP, there is inadequate written description about the structure of all "active drug derivative", and all "small molecule" optionally linked to all "targeting molecule" of all bifunctional molecule having a molecular weight that does not exceed about 5000 daltons for the claimed method because the term "derivative", "small molecule" and "targeting moiety" without the amino acid sequence have no structure. Further, the term "comprising" in claims 24 and 30 expands the bifunctional molecule to include additional amino acids at either or both ends. There is inadequate written description about the undisclosed amino acids to be added, let alone which intracellular protein(s) that the targeting moiety of the bifunctional molecule binds for the claimed method. Further, given the lack of a written description of *any* additional representative species of bifunctional molecule of having a molecular weight that does not exceed about 5000 daltons, all active derivative thereof and all small molecule of the bifunctional molecule and all targeting moiety of all bifunctional molecule that binds to all intracellular protein(s), the claimed method is not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/3/04 have been fully considered but are not found persuasive.

Applicants' position is that the bifunctional molecules employed in the subject methods are extensively described in the specification beginning at page 4 of the specification. This extensive description includes a generic description of these molecules, a description of these molecules in terms of formulas, an extensive description of each of the component pads of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23) as well as a detailed description of how to make these targeted bifunctional molecules (see pages 24 to 28). Furthermore, the specification provides extensive discussion of how to screen bifunctional molecules for desirable activity, and how to use, them for various applications, (including details on dosages, dosage forms and routes of delivery). As such, the bifunctional molecules are fully described in the specification both in

terms of component parts, how to make them, and the resulting bifunctional molecules. The bifunctional molecules are described in structural terms, as well as in terms of functional characteristics arising from those structures - particularly the component parts and how they are linked. One of skill in the art would read the specification and know that the Applicants were in possession of the invention as claimed: a generic method for directing a drug to an intracellular space by linking the drug to a targeting moiety, compared to the drug alone. It is noted that the Examiner's position is apparently premised on the erroneous belief that no additional species beyond the representative FK506, cyclosporin or rapamycin species are described in the specification. See top of page 7 of the Office Action. However, in the Experimental section, additional representative species are disclosed, including chloroquine-containing bifunctional molecules for targeting drugs to melanoma cells (page 34) and quinacrine-containing bifunctional molecules for targeting liver cells (page 34). Accordingly, additional species are disclosed. The Applicants

In response, the claimed method encompasses all bifunctional molecule having a molecule weight that does not exceed about 5000 daltons comprising any targeting moiety optionally joined to any drug moiety such as any active derivative, and any small molecule.

The specification discloses only bifunctional molecule having a drug of interest such as doxorubicin, methotrexaste, vincristine, etoposide covalently linked through a targeting moiety such as FK506 or rapamycin that binds to an intracellular biodistribution modulating protein such as FKBP as a method for directing the biodistribution of a drug upon administering to a host.

With the exception of the specific method of directing the biodistribution of a drug using the specific targeting moiety FK506 or rapamycin of the bifunctional molecule that binds to an intracellular biodistribution modulating protein such as FKBP, there is inadequate written description about the structure of all "active drug derivative", and all "small molecule" optionally linked to all "targeting molecule" of all bifunctional molecule having a molecular weight that does not exceed about 5000 daltons for the claimed method because the term "derivative", "small molecule" and "targeting moiety" without the amino acid sequence have no structure. Further, the term "comprising" in claims 24 and 30 expands the bifunctional molecule to include additional amino acids at either or both ends. There is inadequate written description about the undisclosed amino acids to be added, let alone which intracellular protein(s) that the targeting moiety of the bifunctional molecule binds for the claimed method. Further, given the lack of a written description of *any* additional representative species of bifunctional molecule of having a

molecular weight that does not exceed about 5000 daltons, all active derivative thereof and all small molecule of the bifunctional molecule and all targeting moiety of all bifunctional molecule that binds to all intracellular protein(s), the claimed method is not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 16-18, and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "...said **mammalian** host" in claim 16 line 4 has no antecedent basis in base claim 16, line 3 because line 3 recites "...a host...", not mammalian host.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 16-18, 22-23, 24-26, 30-34, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Szepeshazi et al (Anticancer Drugs 8(10): 974-87, November 1997; PTO 892) as evident by Nagy et al (Proc Natl Acad Sci USA 93: 2464-2469, March 1996; PTO 892) and Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July, 1996: PTO 892).

Szepeshazi *et al* teach a method for directing the biodistribution of a drug that binds to a protein target by administering to a mammalian host such as a mouse an effective amount of various bifunctional molecules such as AN-207 and AN-152 consisting of a drug moiety such as

doxorubicin or an active derivative such as 2-pyrrolino-Doxorubicin and a targeting moiety such as LH-RH analogs that binds to an intracellular biodistribution modulating protein such as LHRH receptors that are located intracellular space (See entire document, abstract, in particular). The reference bifunctional molecule modulates the biodistribution of the doxorubicin to the site of LHRH receptor expressing tumor cells upon administration to the mouse as compared to free drug control and thereby enhances the efficacy of the drug by decreasing cell proliferation and inducing apoptosis of tumor cells (See col. 1, page 975, in particular). The reference drug binds to a protein target such as topoosomierase I and II (See page 985, col. 1, second paragraph, in particular). The reference AN-201 inherently has a molecular weight of 2029.57 daltons as evident by the teachings of Nagy et al who shows that 2-pyrrolino-Doxorubicin has a molecular weight of 595 daltons (See Figure 2, in Proc Natl Acad Sci USA 93: 2464-2469, March 1996) and LH-RH targeting moiety has a molecular weight of 1434.57 daltons (See pGlu-His-Tryp-Ser-Tyr-D-*Lys*-Leu-Arg-Pro-Gly of Figure 1 on page 7271 of Nagy et al in Proc Natl Acad Sci USA 93: 7269-7273, July, 1996; PTO 892). The molecular weight of the targeting molecule can be calculated by adding the molecular weight of 2-pyrrolino-Doxorubicin and the molecular weight of pGlu-His-Tryp-Ser-Tyr-Lys-Leu-Arg-Pro-Gly which, in turn, can be calculated by adding the molecular weight of each amino acids such as Glu has a molecular weight of 147.13, His has a molecular weight of 155.16, Trp has a molecular weight of 204.23, Ser has a molecular weight of 105.09, Tyr has a molecular weight of 181.19, Lys has a molecular weight of 146.19, Leu has a molecular weight of 131.18, Arg has a molecular weight of 174.20, Pro has a molecular weight of 115.13 and Gly has a molecular weight of 75.07). Thus the reference bifunctional molecule has a molecular weight of 2029.57 daltons, which does not exceed about 5000 daltons. The reference bifunctional molecule comprises a glutaric acid spacer (See Figure 1 on page 7271, Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July 1996; PTO 892). The reference bifunctional molecule can also be formed without a linking group by covalently linking the drug moiety via ε amino group of its D-Lys of the targeting molecule LH-RH as evident by the teachings of Nagy et al (See Figure 1 on page 7271, Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July, 1996; PTO 892). The reference bifunctional molecules AN-207 and AN-152 exhibit reduced toxicity and enhanced efficacy upon administering to the host (See entire document, abstract, in particular). Nagy et al further teach that drug targeting is a modern approach that is being tried to overcome the problem of nonselective toxic effects of systemic chemotherapy (See page 7271, col. 2, in particular) and 2-pyrrolino-Dox bifunctional molecule is 500-1000 times more active

than its parent compound (Dox) (See page 7272, col. 2, 1st paragraph, in particular) and much less toxic in vivo (see page 7272, col. 2, last paragraph, in particular). Claim 32 is included in this rejection because Szepeshazi et al teach that the reference bifunctional molecules are intended to treat human having mammary cancers that have LH-RH receptors (See abstract, in particular). Claim 36 is included in this rejection because the reference endogenous biodistribution modulating protein such as LH-RH receptor is an intracellular protein. Thus, the reference teachings anticipate the claimed invention.

11. Claims 39-56 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
August 20, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600